Initial Results of Endothelial Cell Counts after Artisan Lens for Phakic Eyes

An Evaluation of the United States Food and Drug Administration Ophtec Study

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Purpose: To evaluate the endothelial cell count change in eyes implanted with the iris-claw phakic Artisan lens for treatment of moderate to high myopia.

Design: Prospective, multicenter clinical trial.

Participants: The first 765 eyes enrolled at 25 North American sites in the United States Food and Drug Administration Ophtec clinical trial of the myopic Artisan IOL. Outcome analyses of endothelial cell count measurements were based on those obtained before surgery and at 6, 12, and 24 months after surgery performed between October 1998 and December 2001.

Setting: Multiple private and university practices.

Methods: Percentage change in endothelial cell count from baseline to 6, 12, and 24 months were analyzed using specular microscopy. Upper limit of detecting endothelial cell density change was estimated using 3 repeated counts at preoperative and postoperative time frames.

Main Outcome Measures: Percentage change in endothelial cell loss.

Results: The mean preoperative endothelial cell count was 2631±442 cells/mm^2. Percentage change from baseline at 6, 12, and 24 months was −0.09%±16.39%, −0.87%±16.35%, and −0.78%±17.41%. No statistically significative postoperative endothelial cell loss was found. The endothelial cell loss rate was higher among patients who wore spectacles before surgery and was correlated negatively with preoperative endothelial cell density ($P<0.001$). No relationships were noted between endothelial cell loss and either patient age or implant power. A 4.1% repeatability of measurements was found based on the average of 3 repeated counts, whereas single cell count estimates were associated with a 23% accuracy in detecting endothelial cell density change. In a worst-case scenario, adjusting for measurement accuracy, 9% of all eyes were at higher risk of a 10% loss of cell density at 12 months after surgery, although eyes at higher risk were found to have high preoperative endothelial cell counts ($P<0.0001$).

Conclusions: The Artisan iris-claw phakic intraocular lens did not result in significant loss of endothelial cell density up to 2 years after implantation of the myopic Artisan phakic lens. *Ophthalmology 2004;111:309–317 © 2004 by the American Academy of Ophthalmology.*

Several studies have examined changes in endothelial cell counts after implantation of the convex-concave, anterior chamber, Artisan iris-claw phakic lens (Ophtec, Boca Raton, FL) for treatment of high myopia. In 1998, Menezo et al[1] reported data from 111 eyes followed up for 4 years after surgery. They found endothelial cell density was decreased significantly by 3.9% at 6 months and continued to decline thereafter, reaching 6.6% at 1 year, 9.2% at 2 years, 11.7% at 3 years, and 13.4% at 4 years after implantation of the phakic intraocular lens (IOL). Although the percentage of hexagonal cells decreased at 6 months after surgery and the coefficient of variation of cell size was increased, both parameters had returned to preoperative levels by 2 years. In an earlier report involving 94 eyes, the same group of investigators reported an endothelial cell loss rate of 15.8% at 4 years after surgery.[2]

In contrast, Landesz et al[3] even found that mean endothelial cell count had increased at 2 years relative to the preoperative level. Reporting data from 518 eyes enrolled in the European multicenter study of the Artisan phakic intraocular lens, Budo et al[4] reported mean endothelial cell loss rates of 4.8% at 6 months after surgery, 2.4% between 6 months and 1 year, 1.7% between 1 and 2 years, and 0.7% between 2 and 3 years. On the basis of the postoperative refractive results and 6-month postoperative endothelial cell

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counts, the authors concluded that the Artisan lens is a safe, stable, and predictable method for correcting moderate to high myopia.

It has been reported that the specular microscopy measurement method is reproducible within 7%, of which approximately one third is the result of the precision of the techniques and the remaining two thirds is the result of the variance of the endothelial cell population within each eye.[5] Presumably, this level of accuracy may interfere with preoperative and postoperative detection of endothelial cell density change. Interpretations of the clinical significance of data on endothelial cell loss after ocular surgical procedures also should take into consideration the effect of natural age-related cell loss, which has been estimated to average 0.6% per year.[5]

In October 1997, the Food and Drug Administration (FDA) Ophthalmic Devices Panel issued recommendations on guidelines for investigating endothelial cell counts in refractive implant studies.[6] They stated that a maximum rate of surgical loss of 10% is reasonable during the study and that a sample size of 200 subjects would allow the detection of a rate of chronic loss of more than 1.5% per year. The Panel also recommended that the analyses of endothelial cell count changes should be stratified by patient age, that mean rate of loss over time should be calculated via a paired analysis, and that the frequency of eyes with a greater than 10% cell loss should be assessed.

The present study evaluated changes in endothelial cell density after implantation of the Artisan iris-claw phakic lens for myopia in initial eyes enrolled in the US FDA phase III clinical trial. Analysis of our results followed the guidelines of the FDA Ophthalmic Devices Panel while using adjusted percent endothelial changes.[6,7] In addition, we investigated the accuracy of specular microscopy for detecting endothelial cell density change within the clinical study. Data from the actual FDA study collected at different North American sites was provided by Ophtec USA to the authors for an independent analysis of the results.

Materials and Methods

Patients

The ongoing Ophtec USA FDA study of the Artisan iris-claw phakic intraocular lens for myopia is being conducted at 25 investigational sites in North America. All eyes included in this study were the initial eyes enrolled in the US FDA Ophtec study of the Artisan lens for myopia from October 1998 to December 2001. All endothelial cell counts included in this study were taken from all the examinations, up to 2 years after surgery performed from October 1998 to December 2001.

Patients with any of the following findings were excluded from study participation: endothelial cell count ≤2000 cells/mm^2, history of corneal dystrophy or abnormal cornea, abnormalities of the iris, glaucoma, diabetic retinopathy, or chronic uveitis. Three patients with an endothelial cell count lower than 2000 cells/mm^2 were included in the study under a special access program because of the nature of the potential benefit of the lens implantation. Institutional review board or ethics committee approval was obtained at all study centers and all patients gave their informed consent.

As part of the planned safety investigations according to FDA standards, endothelial cell counts were determined before surgery and at follow-up visits for the first 3 years after surgery. Endothelial cell count measurements were performed at the center of the cornea and were obtained using specular microscopy. Specular microscopy systems calculate the endothelial cell density using a recorded picture of the endothelial, then, while identifying the center of each endothelial cell, compute the density of cells per square millimeter on the basis of 70 to 150 identified cells taken from the picture. The cell density is then rounded to the nearest whole number.

For all baseline and follow-up visits conducted between October 1998 and December 1999, endothelial cell counts data were based on a single measurement. To increase accuracy, a protocol revision was made in January 2000 mandating that at all future visits, endothelial cell count data would be based on the average of 3 measurements taken at each visit, including preoperative and all future postoperative examinations.

In addition, preoperative and postoperative data on maximum, minimum, and average cell size, percent of hexagonality, and coefficient of variation of cell size were available from a subgroup of 85 eyes extracted from one study center only.

Method for Calculation of Adjusted Endothelial Cell Count

Endothelial cell loss values were calculated by subtracting a normal yearly cell loss of 0.6% from our results to determine adjusted values. Natural endothelial cell loss as been calculated by Bourne[5] as shown in equation 1:

$$ECD_2 = ECD_1 e^{-rt}, \qquad (1)$$

where ECD is the endothelial cell density in cells per square millimeter of initial (subscript 1) and subsequent (subscript 2) periods; r is the exponential rate of cell loss, estimated to be 0.6%; and t is the time between examination in years. Therefore, the individual adjusted percent endothelial cell change, as shown in equation 2, is:

$$\text{Adjusted percentage change} = \frac{ECD\ (\text{Postop}) - ECD_2}{ECD_2} * 100, \qquad (2)$$

where ECD_2 is estimated with individual preoperative expected natural loss in equation 1.

Accuracy in Assessing Endothelial Cell Density Change

Using the eyes with 3 repeated measurements of endothelial cell counts per examination, an analysis of variance of repeated measurements determined the value of intraclass within-subject variance. Specific repeatability of measurements was determined by dividing the intraclass standard deviation by the mean of the total endothelial cell counts at specific times. The coefficient of repeatability served to estimate the theoretical limit of accuracy while detecting a possible postoperative endothelial cell density change.

Using the examinations with 3 counts, the absolute difference between the highest and the lowest count was computed for each eye. The upper limit of the 95% confidence interval was established as the mean plus 2 times the standard deviation of the absolute maximum difference between counts of each eye. The confidence interval served as the threshold value of required minimum cell count change to identify the eyes at higher risk of endothelial cell density loss. It also was used to determine the

Table 1. Study Completeness

Period	Number of Eyes Examined			Eyes Not Yet Examined	Total Eyes Lost to Follow-up
	*Total**	*1 Count*	*3 Counts*		
Preoperative	765	695	70	NA	NA
6 months after surgery	765	576	189	0	0
12 months after surgery	536	299	237	219	10
24 months after surgery	293	28	265	450	22

NA = not applicable.
*Total of 1 and 3 counts per eye examined.

accuracy of detecting endothelial cell density change while measuring only 1 preoperative and 1 postoperative endothelial cell count.

Statistical Analysis

Microsoft Excel (Redmond, WA) was used for compilation of data. Statistical analysis was performed with SYSTAT 10 (SPSS, Chicago, IL). Paired values were tested using the Wilcoxon sign rank nonparametric test. Preoperative and postoperative mean cell density were tested using Kruskal-Wallis nonparametric test. Uniformity of distribution was evaluated using the Kolmogorov-Smirnov test. Within-subject standard deviation was evaluated using the general linear model analysis of variance with repeated measures. In all tests, a P value of $\leq$0.05 was considered statistically significant.

Results

Study Population

All eyes had a baseline endothelial cell count >2000 cells/mm^2, except for 3 eyes that were granted special access for enrollment from their respective government's regulatory agency.

The power of the implanted Artisan phakic IOL ranged from -5 to -24 diopters (D; mean, -12 ± 3D); preoperative endothelial cell count ranged from 1019 to 4694 cells/mm^2 (mean, 2631$\pm$442 cells/mm^2) based on measurements performed with immersion specular microscopy in 12 eyes (1.6%) and noncontact specular microscopy in 753 eyes (98.4%). Data from the 6-month follow-up visit were available for all eyes, but fewer eyes had reached all required FDA follow-up examinations by December 2001 (Table 1). Twenty-two eyes (2.9%) were lost to follow-up; most eyes did not reach the 24-month postoperative point by December 2001 (Table 1).

Figure 1A, B depicts enrollment and mean preoperative endothelial cell count by investigational site. There was considerable variation between sites in the number of eyes entered into the study (Fig 1A). An analysis of variance showed significant differences in mean preoperative counts (Fig 1B) as well as in mean postoperative counts between investigational sites (P<0.001 for all tests). The mean preoperative count for 49 eyes seen at one site (site 13) was significantly higher compared with the mean count at other sites (P<0.01); this was accounted for by data from 4 eyes having

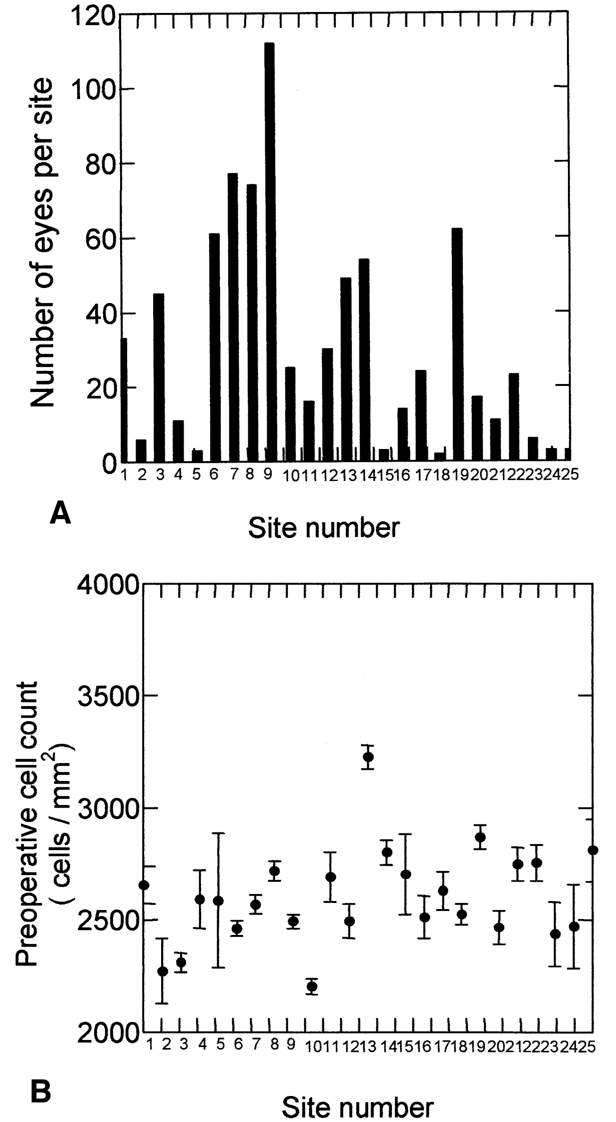

Figure 1. A, Number of eyes evaluated per site. **B,** Mean preoperative endothelial cell count and standard deviation per site.

counts >4000 cells/mm^2. However, it was decided to include the data from site 13 in the analyses, because no scientific reason was given to exclude the data form this site; 1 of 25 sites (P = 0.04) with a preoperative count different from the others is possible by chance alone.

Ophtec USA reported to us that no corneal swelling, or corneal decompensation, was recorded from October 1998 through December 2001 for all eyes at all postoperative follow-ups.

Preoperative and Postoperative Endothelial Cell Counts

Table 2 summarizes data on preoperative and postoperative endothelial cell counts and percentage change for all 765 eyes. Preoperative mean endothelial cell count was 2631$\pm$442 cells/mm^2 (range, 1019–4694 cells/mm^2); it was 2599$\pm$471 cells/mm^2 (range, 1139–7999 cells/mm^2) at 6 months after surgery; 2574$\pm$456 cells/mm^2 (range, 1202–4566 cells/mm^2) at 12

Table 2. Overall Endothelial Cell Density Changes

	Number of Eyes	Cell Density ± Standard Deviation (range) in cells/mm^2	Mean % Individual Change from Preoperative ± Standard Deviation	Mean % Adjusted Change from Preoperative ± Standard Deviation*	Mean % Individual Change from Previous Follow-up ± Standard Deviation†	Mean % Adjusted Change from Previous Follow-up ± Standard Deviation
Before surgery	765	2631 ± 442 (1019–4694)	NA	NA	NA	NA
6 months after surgery	765	2599 ± 471 (1139–7999)	−0.09 ± 16.39	0.21 ± 16.44†	NA	NA
12 months after surgery	536	2574 ± 456 (1202–4566)	−0.87 ± 16.35	−0.28 ± 16.44	0.46 ± 15.99	0.76 ± 16.04†
24 months after surgery	293	2577 ± 495 (1041–5072)	0.78 ± 17.41	0.42 ± 17.41	0.44 ± 18.74	1.04 ± 18.85

NA = not applicable.
*Based on 0.6% per year cell loss (Bourne et al[5]).
†Statistical analysis based on paired measurements of same individual using Wilcoxon sign rank test at $P<0.05$.

months; and 2577±495 cells/mm^2 (range, 1041–5072 cells/mm^2) at 24 months (Table 2). A wide distribution of counts was seen throughout all time periods (Fig 2).

Endothelial Cell Count Baseline Change

Mean percentage of individual count loss from preoperative level was −0.09±16.39% at 6 months after surgery; −0.87±16.35% at 12 months after surgery; and −0.78±17.41% at 24 months after surgery (Table 2). None of those values represented a statistically significant change from baseline using paired analysis. Using the adjusted percentage change data, a significant increase in mean cell population (+0.21%; $P<0.01$) was noted at the 6-month visit, but none of the later values showed any statistically significant change from the preoperative endothelial cell count (Table 2).

Differential endothelial cell count change from baseline ranged from −1819 to 4953 at 6 months after surgery; −1955 to 2150 at 12 months after surgery; −2226 to 2108 at 24 months after

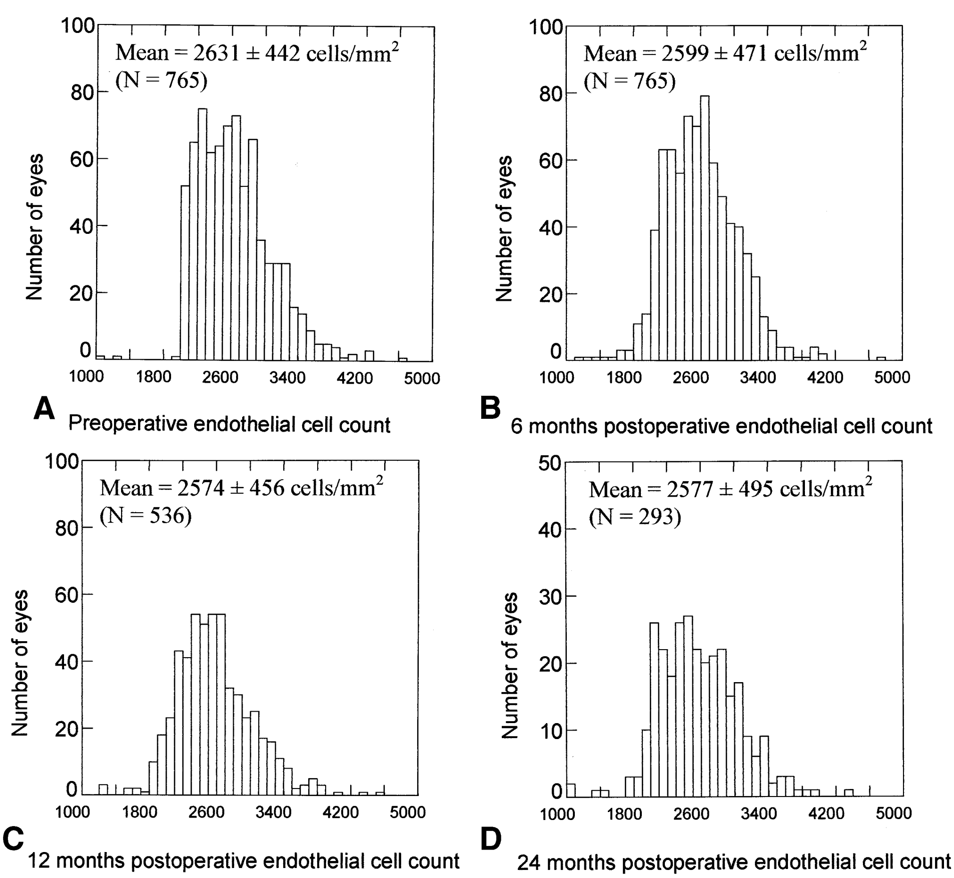

Figure 2. Endothelial cell count (cells/mm^2). **A,** Preoperative. **B,** Six months after surgery. **C,** Twelve months after surgery. **D,** Twenty-four months after surgery.

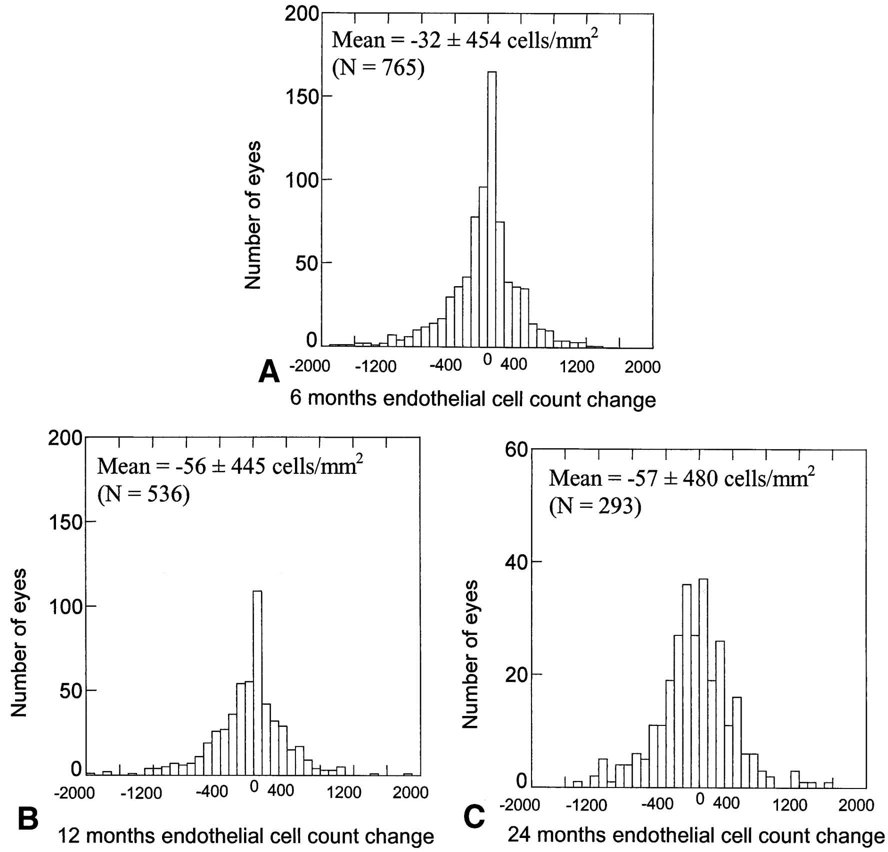

Figure 3. Postoperative difference with preoperative endothelial cell count (cells/mm^2). **A,** Six months after surgery. **B,** Twelve months after surgery. **C,** Twenty-four months after surgery.

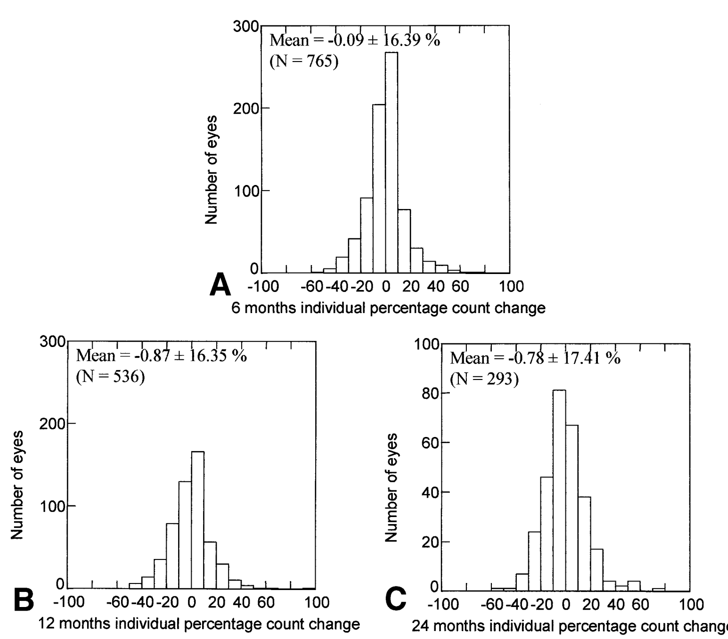

Figure 4. Postoperative percentage of endothelial cell count change (cells/mm^2). **A,** Six months after surgery. **B,** Twelve months after surgery. **C,** Twenty-four months after surgery.

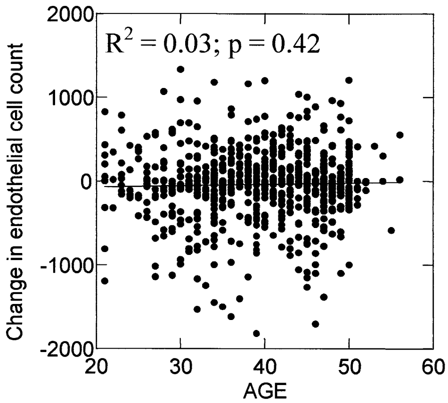

Figure 5. Percentage endothelial cell count change (cells/mm^2) versus age at 6 months after surgery. No significant correlation was found at either 6, 12, or 24 months after surgery on endothelial cell count change versus age.

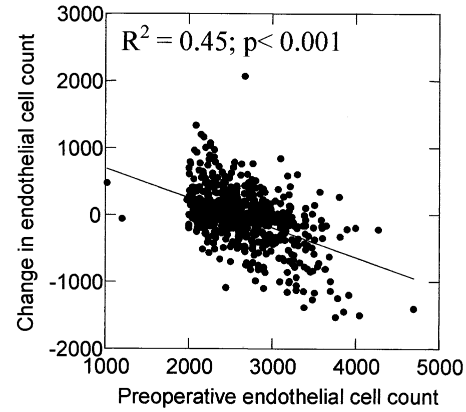

Figure 6. Percentage endothelial cell count change (cells/mm^2) at 6 months after surgery versus initial level of endothelial cell count. Negative significant correlations were found at 6, 12, and 24 months after surgery.

surgery; and −690 to 1068 at 36 months after surgery (Fig 3). Individual percentage of endothelial cell count change ranged from −55% to 162% at 6 months after surgery; −47% to 95% at 12 months after surgery; and −52% to 71% at 24 months after surgery (Fig 4). In effect, very large variations of endothelial cell counts from baseline, positive or negative, were seen throughout the study (Table 2).

The percentage of cell count change between 6 and 12 months and between 12 and 24 months also was calculated. No significant change between these postoperative periods was found using the individual change from the previous follow-up (Table 2). A significant change was found only at 6 months after surgery for the adjusted percentage of change from the previous follow-up; however, the mean change also resulted in an increase of 0.76% in endothelial cell count.

Preoperative correlation of endothelial cell count with implanted lens power was not statistically significative ($R^2 = 0.05$; $P = 0.50$) but was statistically significant with age ($R^2 = 0.05$; $P<0.001$). However, no correlation between percentage change in cell count from baseline to 6 months was found with implant power ($R^2 = 0.001$; $P = 0.28$), patient age ($R^2 = 0.03$; $P = 0.42$; Fig 5), or anterior chamber depth ($R^2 = 0.002$; $P = 0.28$). A highly significant negative correlation was found between preoperative endothelial cell count and the change from baseline to 6, 12, and 24 months (R^2 ranged from 0.42 to 0.50; $P<0.001$ for all correlations); eyes with higher preoperative counts had higher postoperative loss and those with lower counts at baseline had a higher increase in postoperative counts (Fig 6).

As a supplemental analysis, additional analyses were performed to investigate symmetry of cell counts between initial and fellow eyes using 85 eyes from a substudy on endothelial cell count parameters at one study site only. Fellow eye preoperative count significantly correlated with initial eye preoperative count ($R^2 = 0.394$; $P<0.0001$; n = 40). Fellow eye percentage of endothelial cell count change was correlated with the initial eye percentage of change at 6 months after surgery ($R^2 = 0.42$; $P = 0.031$).

Accuracy while Assessing Endothelial Cell Density Change

Using an analysis of variance with repeated measures on eyes with 3 endothelial cell counts (Table 1), the intraclass standard deviation of preoperative counts was 109 cells/mm^2; this resulted in a 4.1% variation in repeatability using the average of 3 endothelial counts (Table 3).

The maximum difference between the lowest and the highest individual count was calculated. The 95% confidence interval resulted in 635 cells/mm^2 using preoperative data, 504 cells/mm^2 using 12-month postoperative data, and 597 and 664 cells/mm^2 using 12- and 24-month postoperative data, respectively (Table 3). Depending on the postoperative period, the estimated percentage of accuracy in detecting density change while using 1 count only ranged from 19% to 25% (Table 3). Within its own time period, the number of eyes for which 1 of the 3 counts was higher or lower than the upper limit of confidence yielded 1.4% of eyes using preoperative data, 4.8% with 6-month postoperative data, 1.3% with 12-month postoperative data, and 3.8% with 24-month postoperative data (Table 3).

Worst-case Scenario

Although the overall data did not show any significant change in mean endothelial cell population after Artisan IOL implantation, we conducted analyses at each follow-up visit to determine what proportion of eyes were outside the upper limit of confidence established by the analysis of single count accuracy. For each eye, we deducted from the preoperative endothelial cell count the upper confidence limit of the counts variation, as found in Table 3, at each postoperative period. Using this methodology, the percentage of eyes at higher risk of endothelial cell count loss was estimated to be 10.5% at 6 months, 9.3% at 12 months, and 8.5% at 24 months, with an estimated mean percentage of cell density change from −10% to −11% (Table 4). Interestingly, mean preoperative cell counts for these eyes were significantly higher than the for all eyes ($P<0.0001$); mean preoperative counts for eyes at higher risk at 6 months after surgery was 3473±498 cells/mm^2 compared with 2631±442 cells/mm^2 for all eyes.

Effect of Preoperative Refractive Correction Method on Endothelial Cell Count

Table 5 summarizes data for analyses investigating effects of preoperative refractive correction method on endothelial cell counts. Among the 765 eyes, 475 wore contact lenses (62%) and 206 used spectacles (27%) for refractive correction before Artisan IOL implantation; the remaining 84 eyes (11%) were excluded from this analysis because they were using both methods of

Table 3. Substudy Results Using 3 Repeated Endothelial Cell Counts within the Initial Series of Eyes

Groups	Number of Eyes with 3 Counts	Mean±Standard Deviation (cells/mm²)	Mean % Individual Change from Preoperative± Standard Deviation*	Repeatability for 3 Counts	Maximum Difference between 3 Counts ±Standard Deviation (cells/mm²)	Upper Limit of 95% Confidence Interval (cells/mm²)	Estimated Percentage of Error in Detecting Count Change while Using 1 Count Only
Before surgery	70	2669±446	NA	4.1%	247±196	635	24%
6 months after surgery	189	2627±410	+0.29±13.14	5.7%	222±141	504	19%
12 months after surgery	237	2630±393	−2.04±13.46	10.7%	215±192	599	23%
24 months after surgery	265	2651±468	−1.11±14.69	3.9%	242±211	664	25%

*No statistical differences based on paired measurements of same individual using Wilcoxon sign rank test at $P < 0.05$.

corrections before surgery. Of the contact lens wearers, 0.7% still used contact lenses 12 months after implantation, no patients continued with spectacle wear after surgery. It was validated that method of preoperative correction had no statistically significant effect on the specific accuracy of endothelial cell count (P = 0.165).

Although there was a large variance of counts, preoperative cell density of contact lens wearers was significantly lower than for spectacles wearers ($P = 0.03$). By 12 months, eyes with a previous history of spectacle wear had a mean −1.15% change from baseline in endothelial cell count, whereas it was −0.55% for previous contact lens wearers; a difference between these two groups was not observed at 24 months after surgery (Table 5). The difference in the percentage of cell loss between these groups was not statistically significant for all postoperative months.

Endothelial Cell Count Parameters

Data for a subgroup of 85 eyes was available for endothelial cell count parameters (Table 6). Average cell size was increased significantly from baseline at both 6 months and 12 months ($P<0.05$ for both values). No significant changes were observed at any follow-up visit in maximum endothelial cell size. Mean minimum cell size increased over time (from 100–131 μm^2), but the change from baseline was statistically significant only after 12 months ($P<0.05$). The percentage of hexagonality remained stable, ranging between 52% and 55% at all visits, and was not affected by any endothelial cell size change. The coefficient of variation changed significantly over time, although it showed an initial increase from baseline at 6 months and then fell to below the baseline value at 12 months after surgery ($P<0.05$). However, the data extracted to perform this analysis had higher mean endothelial cell counts at baseline and at follow-up visits compared with the overall 765 eyes. Mean endothelial cell counts for these eyes were 2848±388 cells/mm² before surgery (n = 85), 2741±322 cells/mm² at 6 months (n = 85) and 2670±402 cells/mm² at 12 months after surgery (n = 60).

Discussion

In our analyses of a large group of eyes enrolled in a multicenter US FDA clinical trial, implantation of the myopic Artisan phakic IOL was not associated with any statistically significant postoperative loss of endothelial cells during up to 2 years of follow-up. Using data unadjusted for the natural age-related decline in endothelial cell density, the present study found mean cell loss rates were <1% at 6, 12, and 24 months after surgery.

Mean endothelial cell loss after phacoemulsification was estimated to be between 8% to 10% at 1 year after surgery.[8,9] Mean endothelial cell loss was not reported to fluctuate 1 year after LASIK, or after PRK.[10–12] Mean endothelial cell loss after keratoplasty was estimated to be 59% from the preoperative level 5 years after surgery.[13] In comparison, the present study did not find any statistically mean loss of endothelial cell count for up to 2 years after surgery.

Even though the corneal-swelling response has been correlated with endothelial cell density,[14] and although

Table 4. Eyes with Estimated Decrease in Endothelial Cell Count

Groups	Percentage of Eyes with Estimated Decrease in Endothelial Cell Count*	Estimation on the Mean Number of Cells Lost ±Standard Deviation (cells/mm²)†	Estimated Percentage of Cell Count Change
6 months after surgery	10.5%	357±311	−11%
12 months after surgery	9.3%	349±311	−10%
24 months after surgery	8.5%	345±326	−10%

*Percentage of eyes with cell loss greater than the estimated percentage error of count change.
†Actual number of endothelial cell change from preoperative count minus upper limit of 95% confidence interval, as found in Table 2. Any postoperative increase in cell density was recorded as zero cell loss.

Table 5. Distribution of Data According to Preoperative Correction Method

	Contact Lens	Spectacles
Implant power	−13.1±2.9 D* (475 eyes)	−12.5±3.0 D* (206 eyes)
Preoperative cell count (cells/mm^2)	2603±421*	2720±469*
6-month cell count (cells/mm^2)	2592±481 (475 eyes)	2667±457 (206 eyes)
Individual percentage count change	+0.69±17.04	−1.45±13.92
Odds ratio of eyes at higher risk†	1.16	1
12-month cell count (cells/mm^2)	2552 ± 448* (330 eyes)	2642 ± 461* (144 eyes)
Individual percentage count change	−0.55 ± 14.99	−1.15 ± 15.02
Odds ratio of eyes at higher risk†	0.73	1
24-month cell count (cells/mm^2)	2577 ± 454 (184 eyes)	2645±584 (70 eyes)
Individual percentage count change	+0.23±15.94	+0.34 ± 18.37
Odds ratio of eyes at higher risk†	0.91	1

D = diopters.
*Differences in means of data between methods of correction.
†The odds ratio of eyes at higher risk were not statically different at 6, 12, and 24 months between contact lens, spectacles, or both types of corrections because of very low statistical power and a small number of eyes being at higher risk.

pump activity has not,[15] the present study does not point to such risks after iris-claw phakic lens implantation.

Initially, the Ophtec FDA study of the Artisan phakic IOL did not include any specific methodology for determining specific accuracy of detecting endothelial cell density change. Using the initial data of the US FDA Ophtec study, it was found that preoperative to postoperative differential counts had large variances using one single count. To increase accuracy for detecting endothelial cell density change, a protocol revision was made in January 2000 mandating that at all endothelial cell count data would be based on the average of 3 measurements taken at each visit, including preoperative and postoperative examinations. Even with this methodology, the present study found a 4.1% accuracy using repeated counts. The present study is not an attempt to validate specular microscopy accuracy, but simply reports on the methodology used to counteract specular microscopy inaccuracies while evaluating postoperative endothelial density change. We hope that future studies will reveal new variables for establishing specular microscopy accuracy.

Noncontact specular microscopy reproducibility previously was estimated to be ±75 cells/mm^2.[16] Bourne et al[5] reported specular microscopy to be reproducible within 7% accuracy. Others authors reported a 2% to 4% variation in cell size per 3 successive counts using noncontact specular microscopy.[17] The present study found specular microscopy repeatability to be 4.1% before surgery; this is also similar to the accuracy found between noncontact and contact specular microscopy.[18] Assuming 4.1% accuracy with a 0.6% annual rate of natural cell loss, endothelial cell density loss at 1 year after Artisan IOL implantation would have to exceed 4.7% to be attributable to the phakic IOL. Using only a single endothelial cell count, 19% to 25% rates of cell loss were estimated to be the threshold value necessary to detect postoperative endothelial cell change (Table 3). To improve the accuracy of endothelial cell count assays in clinical trials, it is mandatory to calculate an average from at least 3 counts. At the same time, given its limited accuracy, currently available technology for measuring endothelial cell density cannot reliably detect an annual chronic 1.5% change in cell population set forth as the limit of acceptability in the proposed FDA guidelines.

Table 6. Substudy of Endothelial Cell Parameters

	Maximum Cell Size (μm^2)	Average Cell Size (μm^2)	Minimum Cell Size (μm^2)	Percent of Hexagonality	Coefficient of Variation
Before surgery	790	356	100	55%	38
6 months after surgery	840	370*	112	52%	41*
12 months after surgery	766	382*	131*	54%	35*

*Statistically significant difference from preoperative data using Wilcoxon sign rank test at $P<0.05$.

Based on recognition of the limited accuracy of endothelial cell count data, we investigated a worst-case scenario to identify eyes at higher risk of endothelial cell loss. We found 10.5% of eyes at 6 months who had cell count losses exceeding normal variations. At 12 months and 24 months after implantation, approximately 9% of eyes were identified as being at higher risk for endothelial cell loss. Endothelial cell density loss did not exceed 11% for these eyes at higher risk. However, the method for assessing this level of risk also yielded up to 5% of error in accuracy. Moreover, the preoperative endothelial cell counts in eyes at higher risk were significantly higher than in the overall group. Therefore, these eyes may have an inherently greater endothelial cell reserve and may be relatively protected from any negative consequences of higher rates of endothelial cell loss.

Few significant changes were observed in the substudy of endothelial cell parameters. Although endothelial cell size increased significantly after surgery because the percentage of hexagonality was not affected, we hypothesize that implantation of the phakic IOL was not associated with the development of pleomorphism.[19] Importantly as well, polymegathism did not seem to occur as coefficient of variation of cell size remained <60%. These results are interesting in that they are consistent with data reported by Menezo et al[1] and would suggest no major change in endothelial cell morphologic features. However, these conclusions are very limited given the small size of the substudy population, its sampling differences compared with the overall population, and the limitations of the technology used for studying pleomorphism and polymegathism.

Although a clear statistical pattern was not found, preoperative method of refractive correction showed a trend to impact on endothelial cell loss. Reversal of distribution between central and peripheral density of endothelial cells has been observed after contact lens removal,[20] and redistribution phenomenon may mask any cell loss resulting from surgically induced endothelial trauma. Consistent with that concept, mean endothelial cell loss at 6 months and 12 months after surgery was higher in previous spectacle wearers compared with eyes using contact lenses for preoperative refractive correction. However, the difference in cell loss rates between groups was not statistically significant, and the pattern of greater cell loss among spectacle wearers was not maintained at 24 months.

Aside from the potential influence of preoperative method of refractive correction on endothelial cell count change, we also investigated possible correlations between endothelial cell count changes and both patient age or implant power. As expected and often reported,[21,22] preoperative cell count was dependent on patient age; postoperative endothelial cell loss, however, was not correlated with age ($P = 0.42$), but with preoperative higher counts ($P<0.001$). Therefore, stratification of endothelial cell loss based on age, or on implant power, would not seem necessary.

This study, based on a large number of eyes, did not reach the conclusion that a significative decrease in endothelial cell count occurs after an Artisan phakic lens implantation for the general population of high myopic eyes.

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